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| 09/402,569 | 03/13/2000 | Peter Kramer | 35280046US00 | 6108 |

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| EXAMINER | |
|---|---|
| BUGAISKY, GABRIELE E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1656 | |

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/402,569 | KRAMER ET AL. | |
| | Examiner | Art Unit | |
| | Gabriele E. BUGAISKY | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



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It is noted that while SEQ ID NO:2 is largely identical to SEQ ID NO:5, it is not a fragment of the larger protein; rather, its 1st three amino acids are unique, then aa4- 105 correspond to aa 1-103 of SEQ ID NO:5, except for aa 101 (ser), which is substituted by ala in SEQ ID NO:5.

***Specification***

The amendment filed 11/04/2003 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amended sequence listing differs from the Sequences presented in figure 2 and the original sequence listing. Specifically, instant SEQ ID NO:5 differs from the original at three amino acids: the figure shows aa153 to be glu, and aas 258 and 269 to each be asp; these positions are gly, ser and ser respectively in SEQ ID NO:5 .

Applicant is required to cancel the new matter in the reply to this Office Action.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12-15 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims as written, do not sufficiently distinguish over nucleic acids, proteins and antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and

the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by page 3, line 1 of specification. See MPEP 2105.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims and are directed to variants of FLIP having anti-apoptotic activity (or DNA encoding FLIP or antibodies directed against FLIP). Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted.

To determine whether there is correspondence between the generic invention of the claims and the written description, is necessary to determine whether the description conveys to one skilled in the relevant art that applicant was in possession of the claimed genus at the time the application was filed. To this end, it is appropriate to inquire whether a number of species

representative of the genus are described in complete structural terms or, alternatively, with reference to other identifying characteristics, *e.g.*, partial structure, chemical properties, functional properties, *etc.* What constitutes a "representative number" of species for any given genus depends in part on whether the level of skill in the art, the teachings in the disclosure, or teachings in the prior art establish predictability as to the structural properties characteristic of the genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The molecule acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Although the specification states that these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class

are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the full-length protein of SEQ ID NO:5 or of SEQ ID NO:2 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus..

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. No sequence of SEQ ID NO:5 was present in the application as filed. The amended sequence listing submitted 11/2003 differs from the Sequences presented in figure 2 and the original sequence listing. Specifically, instant SEQ ID NO:5 differs from the original at three amino acids: the figure shows aa153 to be glu, and aas 258 and 269 to each be asp; these positions are gly, ser and ser respectively in SEQ ID NO:5.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. The specification offers no description of administering the protein in any concentration under any condtions to an individual. Not even successful administration to a cell culture is described (results which could be extrapolated to *in vivo* treatment methods). Furthermore. there is no description that the protein can cross the plasma membrane and have an effect on the apoptotic process. Thus, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claims 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants provide no method of inhibiting apoptosis by determining the expression of a DNA of SEQ ID NO:1.

Claims 12, 14, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the anti-apoptotic polypeptide of SEQ ID NO: 2 or its full length of SEQ ID NO:5, does not reasonably provide enablement for anti-apoptotic proteins bearing a certain degree of sequence similarity to the anti-apoptotic polypeptide of SEQ ID NO: 2 or 5 The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these

claims. It is noted that Applicants have not performed a structural analysis of the protein, as to what regions of the polypeptide are responsible for binding or for anti-apoptotic activity, or as to how the protein is folded. What Applicants have provided is a method of discovering nucleic avoids encoding potential homologs of FLIP, and not anti-apoptotic compounds which are variants of FLIP. A method of identification does not define a compound. With respect to the specific embodiments of claim 14, it is noted that a probe which consists of SEQ ID NO:1 would hybridize to the complement of the coding strand. There is no evidence that the complement encodes a protein and Applicants have not demonstrated that SEQ ID NO:1 is a palindrome.

In *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988), the issue of enablement in molecular biology was considered. There are eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. Although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable. Here, one has description of but two highly conserved variants of a single protein from a single specific organism, but the claims encompass any anti-apoptotic protein which differs by several amino acids and is encoded by any DNA that hybridizes under any condition. . The specification does not teach where one may reasonably expect to obtain such proteins or their encoding nucleic acids. In light of the minimal guidance, the presence of very limited working examples and the breadth of the claims, the Examiner concludes that one has been presented with an invitation to experiment in order to try to obtain the claimed proteins,

nucleic acids and constructs.. Such a task is deemed to constitute undue experimentation.

Claims 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants have provided no method of inhibiting apoptosis by determining the expression of a DNA of SEQ ID NO:1.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 12, and 14-18 are rejected under 35 U.S.C. 102(e) as being anticipated by SHU *et al.* The reference provides the ether recombinant production of CASPER, which is identical to the sequences of figure 2, and varies at only 3 positions from the sequence of instant SEQ ID

NO :5, aa 153 has glu instead of the instant gly, aa 258 has asp instead of the instant ser and aa 269 has asp instead of the instant ser. Further, the reference defines various domains of the protein molecule (see, e.g., column 6, lines 41-52, 62-65, 67; column 7, lines 1-5, 14-24, 65-67, column 8, lines 1-3, 25-35 , column 9, lines 10-26, 20-26, etc). It particularly states in column 7, lines 25-37 )that:

> Full length Casper can induce apoptosis in mammalian cells, whereas Casper (1-435) does not. To ask whether Casper might be involved in Fas or TNF signaling, we determined the effect of Casper (1-435) on TNF- and Fas-mediated apoptosis. When Casper (1-435) was expressed in HeLa cells, it behaved as a dominant negative mutant by inhibiting both TNF- and anti-Fas-induced apoptosis.

With respect to claims 14-18 instant SEQ ID NO:4 is identical to nucleotides 511-1953 of SEQ ID NO: 1 of the patent. Since SEQ ID NO:2 has three additional amino acids at its amino terminus and differs at amino acid 101, the reference is deemed anticipatory only for a protein of claim 1 which differs from SEQ ID NO:2 by one or more amino acids. It is deemed anticipatory for an isolated DNA encoding DNA which differs from SEQ ID NO:1 by several base pairs, for one that hybridizes to SEQ ID NO:1 and for one that comprises the base sequence of SEQ ID NO:4. It is further deemed anticipatory for the claimed recombinant constructs and recombinant method of making a protein,

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shu *et al.*. the reference is discussed in the preceding section; it does not show antibodies specific to CASPER, nor does it show results of hybridization assays.

It does disclose, however, in column 3, lines 21-30:

> The invention provides natural and non-natural Casper-specific binding agents, methods of identifying and making such agents, and their use in diagnosis, therapy and pharmaceutical development. For example, Casper-specific agents are useful in a variety of diagnostic and therapeutic applications. Novel Casper-specific binding agents include Casper-specific receptors, such as somatically recombined protein receptors like specific antibodies or T-cell antigen receptors (see, e.g. Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory). .

The reference also discloses hybridization conditions in column 3, lines 57-67 and column 4, lines 1-9 and states in column 4, lines 30-40 that

> The subject nucleic acids find a wide variety of applications including use as translatable transcripts, hybridization probes, PCR primers, diagnostic nucleic acids, etc.; use in detecting the presence of Casper genes and gene transcripts and in detecting or amplifying nucleic acids encoding additional Casper homologs and structural analogs. In diagnosis, Casper hybridization probes find use in identifying wild-type and mutant Casper alleles in clinical and laboratory

samples. Mutant alleles are used to generate allele-specific oligonucleotide (ASO) probes for high-throughput clinical diagnoses.

Based on the teachings of the reference, one of skill in art thus would be motivated by the teachings of Shu *et al.* to elicit antibodies specific against CASPER and to use the nucleic acids encoding the protein to detect CASPER transcripts, with a reasonable expectation of success.

### *Allowable Subject Matter*

A protein comprising or consisting of SEQ ID NO:2 is deemed free of the prior art.

### *Conclusion*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ni et al. discloses I-Flice proteins and their encoding nucleic acids. Nucleotides 268-1710 of SEQ ID NO:1 are identical to instant SEQ ID NO:4.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. BUGAISKY whose telephone number is (571) 272-0945. The examiner can normally be reached on Tues.- Fri 8:15 AM-1:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gabriele E. BUGAISKY
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Art Unit 1656